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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/500,397	02/08/2000	Gerald Soff	4228-1-1-1	2549

7590 10/21/2002

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	18

DATE MAILED: 10/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/500,397	Applicant(s) SOFF ET AL.	
	Examiner MINH-TAM DAVIS	Art Unit 1642	

-- The MAILING DATE of this communication appears on the c ver sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21 and 23-75* is/are pending in the application.

4a) Of the above claim(s) *1-18, 25-75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-21,23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 11.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 19-21, 23-24 are being examined.

This application contains claims drawn to an invention nonelected with traverse in Paper No.9. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The following are the remaining rejections.

DOUBLE PATENTING

Claims 19, 20, 23 have been rejected under 35 USC 101, obviousness double patenting over claims 65-68 of the pending application SN=08/991761.

Applicant requests that the Examiner hold this rejection in abeyance until the claims are otherwise deemed allowable, at which time Applicant will consider submitting a terminal disclaimer depending on the claims deemed allowable.

Rejection remains. However, the rejection will be hold in abeyance until the time of allowance, if the claims are allowable.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Rejection under 35 USC 112, first paragraph of claims 19-21, 23-24 pertaining to lack of enablement for a method for treating an angiogenic disease remains for reasons already of record in paper No.10.

Applicant argues that cancer is an angiogenic disease, and that Applicant is not required to have a separate disclosure of treatment of each and every type of angiogenic diseases. Applicant recites MPEP 2107.03, stating that Applicant is only required to show a reasonable correlation between the claimed therapeutic use and the biological result after administration of the claimed compounds. Applicant asserts that the present application discloses a cancer patient who received a single treatment with urokinase plasminogen activator alone or in combination with a sulfydryl donor had more than 80% tumor regression as well as a significant increase in plasma angiostatin levels. Applicant further asserts that figures 10-12 demonstrate that plasminogen activators with or without sulfhydryl donors generate angiostatin *in vitro*, and figures 3-5 show that angiostatin generated *in vitro* inhibits cell proliferation *in vitro* as well as angiogenesis *in vivo*.

Applicant further recites MPEP 2106.01, stating that the specification discloses teaches the use of specific plasminogen activators alone or in combination of sulfhydryl donors for treatment of human cancer. Applicant argues the Examiner has not presented a reasonable basis for rejecting the claims.

The recitation of MPEP 2107.03 and MPEP 2106.01 is acknowledged.

Applicant's arguments set forth in paper No.17 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that cancer is a species of angiogenic diseases which include any disease caused by generation of new blood vessel into a tissue or organ, such as ocular neovascularization, arthritis, and diabetes (WO 97/41824, page 1, last paragraph, of record). It is also noted that in Example 8, the patient in case #2 has 80% tumor regression only after being treated with a combination of urokinase and captopril (table 4), and thus it is not clear whether urokinase alone would contribute to the reduction of tumor growth.

Applicant has only shown treatment of a single species of angiogenic diseases, i.e. cancer, using plasminogen activator in combination with a sulfhydryl donor. Applicant however has not shown a reasonable correlation between the claimed treating of angiogenic diseases comprising administration of either a plasminogen activator alone or in combination with a sulfydryl donor and the treatment of cancer after administration of a combination of a plasminogen activator and a sulfydryl donor.

Although figure 17A in the specification discloses that angiostatin is produced in a patient treated with urokinase alone or a combination of urikinase and captopril, the level of angiostatin is barely noticeable. Figure 5B legend on page 6 of the specification however discloses that angiogenesis *in vivo* is inhibited by 10 ug/ml angiostatin produced by PC-3 SFCM. Thus it is questionable that the levels of angiostatin produced by treating a patient with urokinase alone or a combination of urikinase and captopril would be adequate for inhibiting angiogenesis *in vivo*.

In addition, it is noted that as disclosed in the specification, angiostatin is affinity purified from the plasma of patients, and then is used for treating growth of endothelial cells *in vitro*. It is well known in the art that affinity purification would significantly concentrate a purified protein, and thus the concentration used for reducing growth of endothelial cells *in vitro* would not reflect the concentration of angiostatin at the site of angiogenic diseases *in vivo*. Moreover, the *in vitro* condition is different and is not as complex as *in vivo* condition, wherein in *in vitro* conditions, the cells are constantly exposed to angiostatin. Further, the tested endothelial cells are not cells having angiogenesis activity.

On the contrary, Berman et al, of record, clearly teach that administration of a plasminogen activator, urokinase, actually promotes vascularization of the cornea *in vivo*. Thus it is unpredictable that administration of a plasminogen activator alone would be useful for treating any angiogenic disease.

Further, although captopril inhibits angiogenesis and has been used for treating various angiogenic diseases (Volpert et al, of record), the effect on angiogenesis activity by a combination of a plasminogen activator and captopril is unpredictable, because a plasminogen activator such as urokinase and captopril have opposite effects on angiogenesis activity.

In view of the above, it would have been undue experimentation to practice the claimed invention.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

October 5, 2002

SUSAN UNGAR, PH.D
PRIMARY EXAMINER